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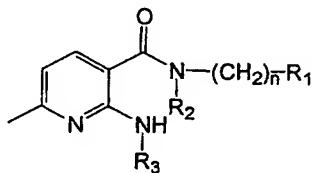
(54) Title: 6-METHYLNICOTINAMIDE DERIVATIVES AS ANTIVIRAL AGENTS

(57) Abstract: The present invention relates to novel 6-methylnicotinamide derivatives and their pharmaceutically acceptable salts, the process for preparing them, and the pharmaceutical compositions containing said compounds as active ingredients. The 6-methyl-nicotinamide derivatives of the present invention exhibit their inhibitory activity against the proliferation of human immunodeficiency virus (HIV) as well as hepatitis B virus (HBV) and Hepatitis C virus (HCV), such that they can be used for hepatitis B, hepatitis C and acquired immune deficiency syndrome (AIDS).

**6-METHYLNICOTINAMIDE DERIVATIVES AS ANTIVIRAL AGENTS****TECHNICAL FIELD**

The present invention relates to novel 6-methylnicotinamide derivatives and pharmaceutical compositions containing said derivatives. More specifically, the present invention relates to novel 6-methylnicotinamide derivatives and their pharmaceutically acceptable salts represented below in formula 1, which have an excellent inhibitory effect on proliferation of hepatitis B virus(HBV), hepatitis C virus(HCV) and human immunodeficiency virus(HIV). The present invention also relates to the process for preparing compounds of formula 1 and the pharmaceutical compositions containing said derivatives as effective ingredients against viruses.

15           Formula 1

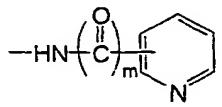


wherein,

R<sub>1</sub> is hydroxy; straight or branched C<sub>1</sub>~C<sub>5</sub> alkyl group; C<sub>3</sub>~C<sub>6</sub> cycloalkyl group which is unsubstituted or substituted with hydroxy, C<sub>2</sub>~C<sub>6</sub> dialkylamino group; saturated or unsaturated 5 or 6 membered heterocyclic compounds

containing 1 to 2 heteroatoms selected from N, O and S which may be unsubstituted or substituted C<sub>1</sub>~C<sub>3</sub> alkyl

group; or



m is an integer of 0 or 1,

R<sub>2</sub> is H or C<sub>1</sub>~C<sub>4</sub> alkyl group;

5 or R<sub>1</sub> and R<sub>2</sub> are joined to form a 5- or 6-membered heterocyclic ring containing 1 to 2 hetero atoms selected from N, O and S,

n is an integer from 0 to 4,

R<sub>3</sub> is 5-indazole or 6-indazole.

10

#### BACKGROUND OF THE INVENTION

Hepatitis B virus (HBV; referred as "HBV" hereinafter) causes acute or chronic hepatitis, which may progress to liver cirrhosis and liver cancer. It is estimated that three hundred million people are infected with HBV in the world (Tiollais & Buendia, *Sci. Am.*, 264, 48, 1991). There has been much research about the molecular biological characteristics of HBV and their relationship to liver diseases in order to find ways to prevent and treat hepatitis B. Various vaccines and diagnostic drugs have been developed and much effort is being channeled into research to find treatment for hepatitis B.

HBV genome consists of genes for polymerase (P), surface

protein (pre-S1, pre-S2 and S), core protein (pre-C and C), and X protein. Of these proteins expressed from HBV genes, polymerase, surface protein, and core protein are structural proteins and X protein has a regulatory function.

5       The gene for HBV polymerase comprises 80% of the whole virus genome and produces a protein of 94kD size with 845 amino acids, which has several functions in the replication of virus genome. This polypeptide includes sequences responsible for activities of protein primer, RNA dependent DNA polymerase, DNA 10 dependent DNA polymerase, and RNase H. Kaplan and his coworkers first discovered reverse transcriptase activities of polymerase, which led to much research in replicating mechanism of HBV.

HBV enters liver when antigenic protein on virion surface is recognized by hepatic cell-specific receptor. Inside the 15 liver cell, DNAs are synthesized by HBV polymerase action, attached to short chain to form complete double helix for HBV genome. Completed double helical DNA genome of HBV produces pre-genomic mRNA and mRNAs of core protein, surface protein, and regulatory protein by the action of RNA polymerase. Using 20 these mRNAs, virus proteins are synthesized. Polymerase has an important function in the production of virus genome, forming a structure called replicasome with core protein and pre-genomic

mRNA. This process is called encapsidation. Polymerase has repeated units of glutamic acid at the 3'-end with high affinity for nucleic acids, which is responsible for facile encapsidation.

When replicasome is formed, (-) DNA strand is synthesized by reverse transcribing action of HBV polymerase and (+) DNA strand is made through the action of DNA dependent DNA polymerase, which in turn produces pre-genomic mRNAs. The whole process is repeated until the pool of more than 200 to 300 genomes is maintained (Tiollais and Buendia, *Scientific American*, 264: 48-54, 1991).

Although HBV and HIV are different viruses, the replication mechanisms during their proliferation have some common steps, namely, the reverse transcription of virus RNA to form DNA and the removal of RNA strand from subsequently formed RNA-DNA hybrid.

Recently, nucleoside compounds such as lamivudine and famvir have been reported to be useful inhibitors of HBV proliferation, although they have been originally developed as therapeutics for the treatment of acquired immune deficiency syndrome (AIDS; referred as "AIDS" hereinafter) and herpes zoster infection (Gerin, J. L, *Hepatology*, 14: 198-199, 1991; Lok, A.

S. P., *J. Viral Hepatitis*, 1: 105-124, 1994; Dienstag, J. L. et al., *New England Journal of Medicine*, 333: 1657-1661, 1995). However, these nucleoside compounds are considered a poor choice for treatment of hepatitis B because of their high cost and side effects such as toxicity, development of resistant virus and recurrence of the disease after stopping treatment. Effort to find therapeutics for hepatitis B among non-nucleoside compounds has been continued and antiviral effects against HBV have been reported for quinolone compounds (EPO 563732, EPO 563734), iridos compounds (KR 94-1886), and terephthalic amide derivatives (KR 96-72384, KR 97-36589, KR 99-5100). In spite of much effort, however, effective drugs for treating hepatitis B have not been developed yet and therapeutic method mainly depends on symptomatic treatment.

Hepatitis C virus (referred as "HCV" hereinafter) is a virus of the flaviviridae family which has a membrane. HCV genome is single stranded (+)-RNA of 9.5 kb in length and express polyprotein comprising of 3010 amino acids. The HCV polyprotein is cleaved co- and posttranslationally by cellular and viral protease to yield 3 structural proteins and 6 nonstructural proteins.

5' - and 3' -terminus of the HCV genome contain untranslated

region (UTR), which highly conserved nucleotide sequence of all most genotype. Recently, it is known that 5'-UTR is a 330~341 nucleotide sequences and 3'-UTR includes 98 nucleotides at the back of poly A, termed to X region which might be played a role 5 of RNA replication and post-translation of virus. Amino end part of HCV genome produces structural proteins Core, E1 and E2 and the other part comprise of non-structural protein. The core is the main structural component of the viral capsid and E1 and E2 comprises of a outer protein. These proteins are cleaved 10 by signal peptidase in endoplasmic reticulum. Serin-type protease NS3 and cofactor NS4A are responsible for the cleavage of nonstructural protein. NS5B protein is a RNA-dependant RNA polymerase. This protein is the most importance enzyme involved in the regulation of HCV replication.

15 It is reported that an infection by HCV is generated from a blood transfusion and community-acquired infection. Approximately 70% of HCV infected individuals will develop chronic hepatitis, of which 20% will progress to severe chonic liverdiseasewithin 5 years. Such higher progression rate, rarely 20 in RNA virus, shows that HCV is a major cause of generating liver cancer. Mechanism studies of the continuous infection of HCV have not been reported. HCV test is therefore carried out in

all blood and the infection opportunity by the blood transfusion is remarkably decreased. But, HCV infection presents a major public health problem worldwide because the community-acquired HCV infection has not regulated yet.

- 5        From the view of retrospective studies, HCV infection uniformly distributes worldwide and 1.5 - 2% of the world's population is infected. Compared to HBV, HCV infection is generally developed in chronic hepatitis and has a high probability of progression to liver cirrhosis and liver cancer.
- 10      Hepatitis C virus that belongs to completely different family cannot be inhibited using B-type vaccine and treatment with  $\alpha$ -interferon. That treatment have not shown a remarkable antiviral effect owing to their variable genotype.

15      Since HCV was discovered in 1987, there has been attempted a lot of research, but remarkably effective drug has not yet developed. Interferon is the unique choice for the treatment so far, but it has confirmed that its medical care rate is less than 30%, HCV is recurred after cessation of its treatment and several interferon-resistant mutant virus generates. So far,

20      there are not characteristic antiviral agents with proliferation inhibitory activity against HCV.

Meanwhile, AIDS is a disease inducing dramatic decrease

in immune function in the body cells and causing various symptoms of infection rarely seen in normal human beings, which spread to the whole body. Human immunodeficiency virus (HIV; referred as "HIV" hereinafter) responsible for AIDS is known to mainly attack helper T cells, which is one of the T cells with regulatory function in the immune system. When helper T cells are infected with HIV virus and undergo necrosis, human immune system cannot function properly. Impairment in immune function subsequently results in fatal infection and development of malignant tumor.

Since AIDS patient has been found in USA in 1981 for the first time, the number increased to more than 850,000 patients in 187 countries in 1993 (WHO 1993 report). WHO predicted that 30 to 40 million more people would be infected with HIV by the year 2000 and 10 to 20 million of them would develop the disease.

At the present time, drugs controlling proliferation of HIV have been most widely used for the treatment of AIDS. Of these, Zidovudine, which had been named Azidothymidine previously, is a drug developed in 1987. Didanosine was developed in 1991 as an alternative medicine for AIDS patients when Zidovudine was either ineffective or could not be used due to side effects. In addition, Zalcitabine was approved for concurrent use with Zidovudine in 1992. These drugs alleviate

symptoms, slow down progression of the disease in the infected individuals to full-blown AIDS, and somewhat extend life span in the patients. These drugs, however, are not able to cure the patients completely and often develop problems such as  
5 resistance and side effects.

In light of these problems, we, inventors of the present invention, tried to develop therapeutics to treat hepatitis B with little chance of toxicity, side effects, and development  
10 of resistant viral strains. We found the compounds with excellent antiviral effect against HBV; synthesized novel 6-methylnicotinamide derivatives represented in formula 1 and completed the invention by showing their dramatic inhibitory effect on proliferation of HIV and HCV as well as of HBV.  
15

It is an object of this invention to provide novel 6-methylnicotinamide derivatives, their pharmaceutically acceptable salts, and their preparation.

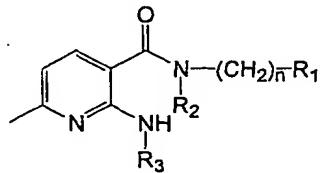
20 It is a further object of this invention to provide a pharmaceutical compositions containing said derivatives with cost effectiveness and little chance of side effects, as a

therapeutic agent as well as a preventive agent for hepatitis B, hepatitis C and acquired immune deficiency syndrome (AIDS).

DETAILED DESCRIPTION OF THE INVENTION

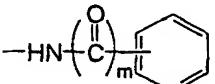
5       The present invention provides novel 6-methylnicotinamide derivatives represented by following formula 1 and their pharmaceutically acceptable salts.

Formula 1



10       wherein,

R<sub>1</sub> is hydroxy; straight or branched C<sub>1</sub>~C<sub>5</sub> alkyl group; C<sub>3</sub>~C<sub>6</sub> cycloalkyl group which is unsubstituted or substituted with hydroxy, C<sub>2</sub>~C<sub>6</sub> dialkylamino group; saturated or unsaturated 5 or 6 membered heterocyclic compounds containing 1 to 2 heteroatoms selected from N, O and S which may be unsubstituted or substituted C<sub>1</sub>~C<sub>3</sub> alkyl

15       group; or ,      m is an integer of 0 or 1,  
R<sub>2</sub> is H or C<sub>1</sub>~C<sub>4</sub> alkyl group;  
or R<sub>1</sub> and R<sub>2</sub> are joined to form a 5- and 6-membered

heterocyclic ring containing 1 to 2 hetero atoms selected from N, O and S,

n is an integer from 0 to 4,

R<sub>3</sub> is 5-indazole or 6-indazole

5 More preferably, wherein,

R<sub>1</sub> is hydroxyl, methyl, isopropyl, t-butyl, cyclopropyl, 4-hydroxyl-1-cyclohexyl, dimethyl amino, 4-morphorinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, 2-pyridyl, 3-pyridyl, 1-imidazolyl, 2-pyridylamino or 3-pyridylcarbonyl amino,

10 R<sub>2</sub> is H,

n is an integer from 0 to 3.

More preferable compounds in accordance with the present invention are as follows;

- 15 1) 2-(1*H*-5-indazolylamino)-*N*-isopropyl-6-methylnicotinamide, (compound of example 1),
- 2) 2-(1*H*-5-indazolylamino)-6-methyl-*N*-(4-morpholinyl)nicotinamide, (compound of example 2),
- 3) *N*-(*trans*-4-hydroxy-1-cyclohexyl)-2-(1*H*-5-indazolylamino)-6-methylnicotinamide, (compound of example 3),
- 20 4) 2-(1*H*-5-indazolylamino)-6-methyl-*N*-(3-pyridyl)nicotinamide, (compound of example 4),

- 5) 2-(1*H*-5-indazolylamino)-6-methyl-*N*-(3-pyridylmethyl)nicotinamide, (compound of example 5),
- 6) 2-(1*H*-5-indazolylamino)-6-methyl-*N*-(2-pyridylethyl)nicotinamide, (compound of example 6),
- 5 7) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-methylnicotinamide, (compound of example 7),
- 8) 2-(1*H*-6-indazolylamino)-*N*-isopropyl-6-methylnicotinamide, (compound of example 8),
- 9) *N*-(*t*-butyl)-2-(1*H*-6-indazolylamino)-6-methylnicotinamide, (compound of example 9),
- 10 10) *N*-(2-hydroxyethyl)-2-(1*H*-6-indazolylamino)-6-methylnicotinamide, (compound of example 10),
- 11) *N*-cyclopropyl-2-(1*H*-6-indazolylamino)-6-methylnicotinamide, (compound of example 11),
- 15 12) *N*-[2-(dimethylamino)ethyl]-2-(1*H*-6-indazolylamino)-6-methylnicotinamide, (compound of example 12),
- 13) *N*-[2-(diethylamino)ethyl]-2-(1*H*-6-indazolylamino)-6-methylnicotinamide, (compound of example 13),
- 14) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-[2-(4-morpholinyl)ethyl]nicotinamide, (compound of example 14),
- 20 15) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-[2-(1-piperidinyl)ethyl]nicotinamide, (compound of example 15),

- 16) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(4-morpholinyl)nicotinamide, (compound of example 16),
- 17) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(4-methyl-1-piperazinyl)nicotinamide, (compound of example 17),
- 5 18) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(3-pyridyl)nicotinamide, (compound of example 18),
- 19) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(3-pyridylmethyl)nicotinamide, (compound of example 19),
- 20) *N*-[3-(1*H*-1-imidazolyl)propyl]-2-(1*H*-6-indazolylamino)-6-methylnicotinamide, (compound of example 20),
- 10 21) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(2-pyridyl)-3-pyridinecarbohydrazide, (compound of example 21),
- 22) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(3-pyridylcarbonyl)-3-pyridinecarbohydrazide, (compound of example 22),
- 15 23) 2-(1*H*-6-indazolylamino)-6-methyl-3-(4-morpholinylcarbonyl)pyridine, (compound of example 23).

The compounds according to the present invention have an inhibitory effect on HIV proliferation as well as HBV, HCV since containing 5-indazolylamino or 6-indazolylamino as a substituent of 6-methylnicotinamide derivatives.

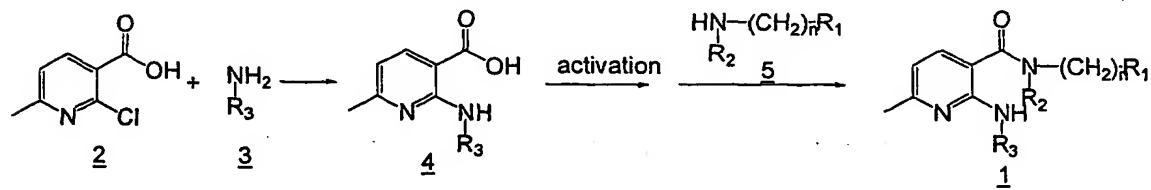
The compounds represented by formula 1 of the present

invention may be utilized in the form of salts and the acid addition salts prepared by adding pharmaceutically acceptable free acids are useful. Compounds of formula 1 may be changed to the corresponding acid addition salts according to the general practices in this field. Both inorganic and organic acids may be used as free acids in this case. Among inorganic acids, hydrochloric acid, hydrobromic acid, sulfuric acid, or phosphoric acid may be used. Among organic acids, citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, benzoic acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, 4-toluenesulfonic acid, galacturonic acid, embonic acid, glutamic acid or aspartic acid may be used.

15

The present invention also provides a process for preparing 6-methylnicotinamide derivatives of formula 1, represented by scheme 1 as follows:

Scheme 1



wherein, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and n are as defined in formula 1.

The process for preparing in the present invention comprises the following steps of:

- 5        1) preparing of 6-methylnicotinic acid derivatives (4) substituted with aminoindazole by reacting 2-chloro-6-methylnicotinic acid (2) with 5-aminoindazole or 6-aminoindazole (3) in the presence of a base; and,
- 10      2) preparing of 6-methylnicotinamide derivatives of formula 1 by activating the 6-methylnicotinic derivatives (4) prepared in step 1, and then reacting the compounds of formula 4 with amine compound (5).

A detail description will be stepwise given of the method 15 for preparing 6-methylnicotinamide derivatives of the present invention.

Chemical reagents used as starting and reaction materials in the step 1 and 2 of the scheme 1, namely, 2-chloro-6-methylnicotinic acid (2), 5-aminoindazole (3), 20 6-aminoindazole (3) and amine compound (5), are commercially available and may be purchased.

The amine compound (5) in the step 2 is also used to

introduce a constituent ( $R-NR_2-(CH_2)_n-R_1$ ) into the desired compound of formula 1 and an appropriate amine compound should be selected depending on the substituent desired, which can be easily done by one with general knowledge in the technical field.

5 In the step 1, it is preferably used tertiary organic base having weak basicity such as pyridine, picoline, lutidine, *N,N*-dimethylaniline, 4- dimethylaminopyridine, as a base.

10 In the step 2, compounds of the formula 1 is prepared by reacting with amine compound (5) after activating 6-methylnicotinic acid derivatives (4) obtained by the step 1.

15 In activating process, 6-methylnicotinic acid derivatives are activated by adding a bit excess thionyl chloride to 6-methylnicotinic acid derivatives (4), subsequently heating, or, by Vilsmeier reagent prepared for heating thionyl chloride and *N,N*-dimethylformamide.

For a solvent, a single or a mixture of solvents selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran and ether is preferable.

20 The reaction temperature is preferably 0~20 °C.

Furthermore, the present invention provides the pharmaceutical compositions of therapeutics comprising 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts of formula 1 as effective ingredients to prevent

and treat hepatitis B.

The present invention also provides the pharmaceutical compositions of therapeutics, comprising 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts of formula 1 as effective ingredients to prevent and treat hepatitis C.

An inhibitor of RNA-dependant RNA-polymerase in the HCV, can essentially inhibit on HCV proliferation, and the compounds of the present invention is therefore expected to be useful for therapeutic agents on Hepatitis C with low toxicity since the RNA-dependant RNA-polymerase is not detected yet in human body cell.

6-methylnicotinamide derivatives of formula 1 in present invention have an inhibitory effect on proliferation of both HIV and HBV because they interfere with removal of RNA strand from RNA-DNA hybrid formed during the reverse transcription of viral RNA to DNA, which is a common step in the replication mechanism of the two viruses.

Therefore, the present invention also provides the pharmaceutical compositions of therapeutics for preventing and treating AIDS, which comprise 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts of formula 1 as

effective ingredients.

Compounds of formula 1 may be taken orally as well as through other routes in clinical uses; for example, it may be administered intravenously, subcutaneously, intraperitoneally, locally and 5 in the form of general drugs.

For clinical use of drugs with the pharmaceutical compositions of the present invention, compounds of formula 1 may be mixed with pharmaceutically acceptable excipients and made into various pharmaceutically acceptable forms; for example, 10 tablets, capsules, troches, solutions, suspensions for oral administration; injection solutions, suspensions, and dried powder to be mixed with distilled water for the formulation of instant injection solution.

Effective dosage for compound of formula 1 is generally 15 10~500 mg/kg, preferably 50~300 mg/kg for adults, which may be divided into several doses, preferably into 1~6 doses per day if deemed appropriate by a doctor or a pharmacist.

Hereinafter the present invention describes in more detail. However, it will be appreciated that those skilled in the art, 20 on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

EXAMPLE

<Preparation Example 1> Preparation of

**2-(1*H*-5-indazolylamino)-6-methylnicotinic acid**

To the solution of 2-chloro-6-methylnicotinic acid 10 g  
5 and 5-aminoindazole (8.6 g) in methanol 70 ml was added pyridine  
10 ml, and then the solution was reacted at 40~50 °C for 3 days.  
The reaction mixture was cooled, added H<sub>2</sub>O 35 ml slowly at 20 °C,  
and then stirred for 2 hr. The reaction mixture was filtered  
to obtaining a solid, and the solid was washed with 50% methaoil  
10 15 ml to obtaining a solid product. The desired compound(13 g,  
yield 83%) was obtained by drying of the solid product at 40~50°C  
*in vacuo*.

m.p. : 252~254 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm: δ 2.40(s, 3H), 6.66(d, 1H), 7.41(m,  
15 2H), 7.96(d, 1H), 8.09(d, 1H), 8.31(q, 1H), 10.42(s, 1H), 13.13(br  
S, 2H)

<Preparation Example 2> Preparation of

**2-(1*H*-6-indazolylamino)-6-methylnicotinic acid**

To the solution of 2-chloro-6-methylnicotinic acid 10 g  
20 and 6-aminoindazole 8.6 g in methanol 100 ml was added pyridine  
9.5ml, and then the solution was refluxed for 3 days. The reaction  
mixture was cooled, added H<sub>2</sub>O 30 ml slowly at 20 °C, and then

stirred for 2 hr. The reaction mixture was filtered and the obtained solid was washed with methanol 20 ml. The desired compound (13.3 g, yield 85%) was obtained by drying of the solid product at 40~50 °C in vacuo.

5 m.p. : 273~274 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm: δ 2.49(s, 3H), 6.75(d, 1H), 7.01(d, 1H), 7.65(m, 1H), 7.93(s, 1H), 8.14(m, 1H), 8.53(s, 1H), 10.70(s, 1H), 13.13(br s, 2H)

<b>&lt;Example</b>	<b>1&gt;</b>	<b>Preparation</b>	<b>of</b>
10	2-(1H-5-indazolylamino)-N-isopropyl-6-methylnicotinamide		

To the solution of methylene chloride (120 ml) was added N,N-dimethylformamide (2.3 ml) and thionyl chloride (2.7 ml) and the solution was refluxed for 2 hr. 2-(1H-5-indazolylamino)-6-methylnicotinic acid 4g obtained by preparation example 1 was added to the solution and the reaction mixture was refluxed for 2 hr. The reaction mixture was cooled and isopropyl amine 6 ml was slowly added. After stirring for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was diluted with methanol 50 ml and H<sub>2</sub>O 50 ml and 20 3N-NaOH aqueous solution was added to adjust to pH=9~10. The solution was stirred at 20°C for 30 min. and filtered to the solid. The solid was recrystallized with chloroform : isopropyl

ether = 1: 10 to obtain the desired compound (3.6 g, yield 78%).

m.p. : 203~206 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 1.17(d, 6H), 2.40(s, 3H),  
4.12(m, 1H), 6.65(d, 1H), 7.35(d, 1H), 7.43(d, 1H), 7.96(s, 1H),  
5 8.00(d, 1H), 8.34(d, 2H), 11.01(s, 1H), 12.89(s, 1H)

**<Example 2> Preparation of  
2-(1H-5-indazolylamino)-6-methyl-N-(4-morpholinyl)nicotinamide**

To the solution of methylene chloride 30 ml was added  
10 N,N-dimethylformamide 0.34 ml and thionyl chloride 0.4 ml and  
the solution was refluxed for 2 hr.  
2-(1H-5-indazolylamino)-6-methylnicotinic acid 0.6 g obtained  
by preparation example 1 was added to the solution and the reaction  
mixture was refluxed for 2 hr. The reaction mixture was cooled  
15 and 4-aminomorpholine 1 ml was slowly added. After stirring for  
1 hr, the reaction mixture was concentrated under reduced pressure.  
The residue was diluted with H<sub>2</sub>O 20 ml and 3N-NaOH aqueous solution  
was added to adjust to pH=9~10. The solution was extracted with  
chloroform 30 ml. The organic layer was separated, concentrated  
20 under reduced pressure and the concentrate was purified by column  
chromatography (chloroform : isopropanol=10:1 (v/v)), and then  
recrystallized with ether to obtain the desired compound (0.45

g, yield 57%).

m.p. : 257~260 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.40(s, 3H), 2.87(br s, 4H),  
3.66(br s, 4H), 6.65(d, 1H), 7.35(d, 1H), 7.44(d, 1H), 7.91(d,  
5 1H), 7.97(s, 1H), 8.33(s, 1H), 9.63(s, 1H), 10.66(s, 1H), 12.90(s,  
1H)

<Example 3> Preparation of  
**N-(trans-4-hydroxy-1-cyclohexyl)-2-(1H-5-indazolylamino)-6-methylnicotinamide**

To the solution of *N,N*-dimethylformamide 0.23 ml in methylene chloride 20 ml was added thionyl chloride 0.27 ml, the solution was refluxed for 2 hr. 2-(1H-5-indazolylamino)-6-methylnicotinic acid 0.4 g obtained by preparation example 1 was added and the solution was refluxed for 2 hr. The reaction mixture was cooled and to the reaction mixture were added *trans*-4-aminocyclohexanol chloride (salt) 0.7 g and triethylamine 0.8 ml slowly at 0~5°C and then the mixture was stirred for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was diluted with methanol 7 ml and H<sub>2</sub>O 12 ml and 3N-NaOH aqueous solution was added to adjust to pH=10. After stirring at 20°C for 30 min, the mixture was filtered to obtain the solid product. The solid

product was washed with H<sub>2</sub>O, recrystallized with methanol and methylene chloride to obtain the desired compound (0.35 g, yield 64%).

m.p. : > 280 °C

5           <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 1.19 (m, 2H), 1.32 (m, 2H), 1.80 (m, 4H), 2.39 (s, 3H), 3.38 (d, 1H), 3.86 (br s, 1H), 4.58 (d, 1H), 6.64 (q, 1H), 7.35 (d, 1H), 7.43 (m, 1H), 7.96 (m, 2H), 8.28 (t, 2H), 10.96 (d, 1H), 12.90 (s, 1H)

10       **<Example 4> Preparation of  
2-(1H-5-indazolylamino)-6-methyl-N-(3-pyridyl)nicotinamide**

The desired compound (yield 53%) was obtained by performing at the same manner as example 2, except for using 3-aminopyridine instead of 4-aminomorpholine.

m.p. : 237~240 °C

15       <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.44 (s, 3H), 6.76 (d, 2H), 7.39 (m, 3H), 7.98 (s, 1H), 8.12 (d, 1H), 8.18 (q, 1H), 8.31 (t, 2H), 8.87 (s, 1H), 10.47 (s, 1H), 12.92 (s, 1H)

20       **<Example 5> Preparation of  
2-(1H-5-indazolylamino)-6-methyl-N-(3-pyridylmethyl)nicotinamide**

The desired compound was obtained at the same manner as example 1, except for using 3-(aminomethyl)pyridine instead of

isopropylamine.

m.p. : 95~97 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.40(s, 3H), 4.50(br s, 2H), 6.69(d, 1H), 7.30(m, 3H), 7.74(s, 1H), 7.96(s, 1H), 8.05(d, 1H), 8.32(s, 5 1H), 8.46(s, 1H), 8.57(s, 1H), 9.23(s, 1H), 10.94(s, 1H), 12.93(s, 1H)

**<Example 6> Preparation of  
2-(1H-5-indazolylamino)-6-methyl-N-(2-pyridylethyl)nicotina  
mide**

10 The desired compound (yield 73%) was synthesized at the same manner as the example 2, except for using 2-(2-aminoethyl)pyridine instead of 4-aminomorpholine. The crude product was purified by column chromatography (hexane:ethyl acetate:methanol=5:5:1(v/v)) and recrystallized with isopropyl ether.

m.p. : 98~99 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.40(s, 3H), 3.02(br s, 2H), 3.62(br s, 2H), 6.65(d, 1H), 7.20(d, 1H), 7.28(d, 1H), 7.36(d, 1H), 7.44(d, 1H), 7.68(t, 1H), 7.92(d, 1H), 7.94(s, 1H), 8.33(s, 20 1H), 8.49(s, 1H), 8.74(s, 1H), 10.96(s, 1H), 12.90(s, 1H)

**<Example 7> Preparation of  
2-(1H-6-indazolylamino)-6-methyl-N-methylnicotinamide**

To the solution of  
2-(1H-6-indazolylamino)-6-methylnicotinic acid 0.9 g obtained  
by preparation example 2 in acetonitrile 30 ml was added thionyl  
chloride 0.75 ml slowly. After stirring at 70°C for 1 hr, the  
5 mixture was cooled. methylamine(40% methanol solution) 3 ml was  
slowly added at 0~5 °C and the mixture was reacted for 30 min.  
The reaction mixture was diluted with H<sub>2</sub>O 30 ml and acetonitrile  
was removed under reduced pressure. The solution was extracted  
with chloroform 50 ml. The organic layer was separated,  
10 concentrated under reduced pressure and residue was  
recrystallized with methylene chloride: ether=2:1 (v/v) to  
obtain the desired compound (0.67 g, yield 71%).

m.p. : 210~211 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49(s, 3H), 2.81(s, 3H),  
15 6.76(d, 1H), 6.95(d, 1H), 7.62(d, 1H), 7.91(s, 1H), 8.01(dd, 1H),  
8.53(s, 1H), 8.69(br s, 1H), 11.36(s, 1H), 12.81(br s 1H)

**<Example 8> Preparation of  
2-(1H-6-indazolylamino)-N-isopropyl-6-methylnicotinamide**

To the solution of  
20 2-(1H-6-indazolylamino)-6-methylnicotinic acid 0.9 g obtained  
by preparation example 2 in acetonitrile 30 ml was added thionyl  
chloride 0.75 ml slowly. After stirring at 70°C for 1 hr, the

solution was cooled. To the reaction mixture was added isopropylamine 2.5 ml slowly at 0~5 °C and the mixture was reacted for 30 min. The reaction mixture was diluted with H<sub>2</sub>O 30 ml and then concentrated under reduced pressure. To the residue was 5 added 3N-NaOH aqueous solution to adjust to pH = 9~9.5, and the mixture was stirred for 1 hr and then filtered to obtain a solid product. The solid product was washed with H<sub>2</sub>O, recrystallised with methylene chloride and ether 1:4 (v/v) to obtain the desired compound (0.78 g, yield 75%).

10 m.p. : 212~214 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 1.86(m, 6H), 2.49(s, 3H), 4.15(m, 1H), 6.76(d, 1H), 6.95(d, 1H), 7.61(dd, 1H), 7.92(s, 1H), 8.07(dd, 1H), 8.44(br s, 1H), 8.53(s, 1H), 11.31(s, 1H), 12.86(br s, 1H)

<Example 9> Preparation of

15 N-(t-butyl)-2-(1H-6-indazolylamino)-6-methylnicotinamide

To the solution of 2-(1H-6-indazolylamino)-6-methylnicotinic acid 1.0 g obtained by preparation example 2 in acetonitrile 30 ml was added thionyl chloride 0.83 ml slowly. The solution was reacted at 70°C for 20 1 hr and t-butyl amine 3 ml was slowly added at 0~5 °C. After stirring for 30 min., Methanol 30 ml was added to the reaction mixture at 20 °C and the mixture was filtered. The filtrate

concentrated under reduced pressure was diluted with methanol 5 ml and precipitated in H<sub>2</sub>O 30 ml. The mixture was stirred for 1 hr, filtered and washed with H<sub>2</sub>O 5 ml. The obtained solid product was purified by column chromatography (n-Hexane: ethyl acetate: methanol=10:5:1 (v/v)) to obtain the desired compound (0.75 g, yield 62%).

m.p. : 107~109 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 1.39 (s, 9H), 2.49 (s, 3H), 6.72 (d, 1H), 6.93 (d, 1H), 7.60 (d, 1H), 7.90 (s, 1H), 7.99 (m, 2H), 8.48 (s, 1H), 11.04 (s, 1H), 12.78 (br s, 1H)

**<Example 10> Preparation of N-(2-hydroxyethyl)-2-(1H-6-indazolylamino)-6-methylnicotinamide**

The desired compound (yield 58%) was prepared at the same manner as example 9, except for using ethanol amine instead of t-butyl amine.

m.p. : 217~220 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49 (s, 3H), 3.33 (m, 2H), 3.52 (m, 2H), 4.77 (br s, 1H), 6.75 (d, 1H), 6.93 (d, 1H), 7.60 (d, 1H), 7.90 (s, 1H), 8.06 (d, 1H), 8.52 (s, 1H), 8.67 (br s, 1H), 11.29 (s, 1H), 12.79 (br s, 1H)

**<Example 11> Preparation of**

**N-cyclopropyl-2-(1H-6-indazolylamino)-6-methylnicotinamide**

To the solution of 2-(1H-6-indazolylamino)-6-methylnicotinic acid 1.0 g obtained by preparation example 2 in acetonitrile 30 ml was added thionyl chloride 0.83 ml slowly. The solution was reacted at 70 °C for 1 hr and then cooled. To the reaction mixture was added cyclopropyl amine 2.3 ml slowly at 0~5 °C and the mixture was reacted for 30 min. The reaction mixture was diluted with methanol 10 ml and methylene chloride 10 ml and filtered to remove the undissolving inevitable impurity. The residue concentrated under reduced pressure, was dissolved in methanol 10 ml, added H<sub>2</sub>O 40 ml and 3N-NaOH aqueous solution 2 ml. After stirring for 1 hr, the mixture was filtered and then washed with H<sub>2</sub>O. The obtained solid product was recrystallized with chloroform: ether=1:5 (v/v) to obtain the desired compound (0.79 g, yield 69%).

m.p. : 189~190 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 0.59(m, 2H), 0.70(m, 2H), 2.49(s, 3H), 2.85(m, 1H), 6.73(d, 1H), 6.95(d, 1H), 7.60(d, 1H), 7.90(s, 1H), 7.99(d, 1H), 8.52(s, 1H), 8.64(br s, 1H), 11.31(s, 1H), 12.80(br s, 1H)

**<Example 12> Preparation of**

**N-[2-(dimethylamino)ethyl]-2-(1H-6-indazolylamino)-6-methyl  
nicotinamide**

The desired compound (yield 66%) was obtained by performing at the same manner as example 9, except for using  
 5      N,N-dimethylethylene diamine instead of t-butyl amine.

m.p. : 182~183 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.21(s, 6H), 2.49(s, 3H), 3.38(m, 4H), 6.77(d, 1H), 6.96(d, 1H), 7.62(d, 1H), 7.92(s, 1H), 8.04(d, 1H), 8.52(s, 1H), 8.66(br s, 1H), 11.29(s, 1H), 12.81(br s, 1H)

10      <Example                          13>                          Preparation                          of  
**N-[2-(diethylamino)ethyl]-2-(1H-6-indazolylamino)-6-methyl  
nicotinamide**

The desired compound (yield 58%) was obtained by performing at the same manner as example 9, except for using  
 15      N,N-diethylethylene diamine instead of t-butyl amine.

m.p. : 154~155 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 0.99(m, 6H), 2.45~2.55(m, 9H), 3.35(m, 2H), 6.77(d, 1H), 6.95(d, 1H), 7.62(d, 1H), 7.92(s, 1H), 8.02(d, 1H), 8.52(s, 1H), 8.66(br s, 1H), 11.28(s, 1H), 12.82(br  
 20      s, 1H)

<Example                          14>                          Preparation                          of  
**2-(1H-6-indazolylamino)-6-methyl-N-[2-(4-morpholinyl)ethyl]**

**nicotinamide**

To the solution of 2-(1H-6-indazolylamino)-6-methylnicotinic acid 1.0 g obtained by preparation example 2 in acetonitrile 40 ml was added thionyl chloride 0.83 ml slowly and the solution was reacted at 70 °C for 1 hr. The reaction mixture was cooled and 4-(2-aminoethyl)morpholine 4.0 ml was slowly added at 0~5 °C. After stirring for 30 min., the reaction mixture was filtered at 20 °C and washed with acetonitrile 5 ml to remove an undissolving inevitable impurity. The filtrate concentrated under reduced pressure, was dissolved in methylene chloride 40 ml and washed with NaCO<sub>3</sub> aqueous solution and H<sub>2</sub>O. The organic layer was concentrated under reduced pressure and recrystallized with chloroform : ether = 1:3 (v/v) to obtain the desired compound (1.04 g, yield 73%).

m.p. : 165~168 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.42 (m, 4H), 2.49 (s, 3H), 3.33~3.42 (m, 4H), 3.57 (m, 4H), 6.77 (d, 1H), 6.95 (d, 1H), 7.62 (d, 1H), 7.92 (s, 1H), 8.03 (d, 1H), 8.52 (s, 1H), 8.66 (br s, 1H), 11.27 (s, 1H), 12.81 (br s, 1H)

**<Example 15> Preparation of  
2-(1H-6-indazolylamino)-6-methyl-N-[2-(1-piperidinyl)ethyl]**

**nicotinamide**

The desired compound (yield 62%) was obtained by performing at the same manner as example 9, except for using 1-(2-aminoethyl)piperidine instead of *t*-butyl amine.

5 m.p. : 177~179 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 1.37 (m, 2H), 1.50 (m, 4H), 2.49 (m, 7H), 3.35 (m, 4H), 6.77 (d, 1H), 6.95 (d, 1H), 7.62 (d, 1H), 7.92 (s, 1H), 8.02 (d, 1H), 8.52 (s, 1H), 8.65 (br s, 1H), 11.27 (s, 1H), 12.81 (br s, 1H)

10 <Example 16> Preparation of  
2-(1*H*-6-indazolylamino)-6-methyl-N-(4-morpholinyl)nicotinamide

The desired compound (yield 70%) was prepared at the same manner as example 14, except for using 4-aminomorpholine instead 15 of 4-(2-aminoethyl)morpholine. Then crude product was purified by recrystallization with ethyl acetate: hexane=1:1(v/v).

m.p. : 265~268 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.48 (s, 3H), 2.88 (s, 4H), 3.67 (s, 4H), 6.75 (d, 1H), 6.95 (d, 1H), 7.60 (d, 1H), 7.90 (s, 1H), 7.96 (d, 1H), 8.50 (s, 1H), 9.69 (br s, 1H), 10.93 (s, 1H), 12.80 (br s, 1H)

<Example 17> Preparation of  
2-(1*H*-6-indazolylamino)-6-methyl-N-(4-methyl-1-piperazinyl)

**nicotinamide**

The desired compound (yield 67%) was obtained by performing at the same manner as example 9, except for using 1-amino-4-methylpiperazine instead of *t*-butyl amine.

5 m.p. : 263~265 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.20(s, 3H), 2.49(s, 4H), 2.89(s, 4H), 3.36(s, 3H), 6.76(d, 1H), 6.98(d, 1H), 7.63(d, 1H), 7.92(s, 1H), 7.98(d, 1H), 8.52(s, 1H), 9.62(br s, 1H), 10.92(s, 1H), 12.83(br s, 1H)

10 <Example 18> Preparation of  
**2-(1*H*-6-indazolylamino)-6-methyl-N-(3-pyridyl)nicotinamide**

The desired compound (yield 51%) was prepared at the same manner as example 11, except for using 3-aminopyridine instead of cyclopropyl amine. Then crude product was purified by 15 recrystallization with methylene chloride: ether=1:2(v/v).

m.p. : > 280 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49(s, 3H), 6.83(d, 1H), 6.97(d, 1H), 7.39(dd, 1H), 7.59(d, 1H), 7.89(s, 1H), 8.11(d, 1H), 8.21(d, 1H), 8.31(m, 1H), 8.47(s, 1H), 8.85(d, 1H), 10.52(br s, 1H), 20 10.68(s, 1H), 12.81(br s, 1H)

20 <Example 19> Preparation of  
**2-(1*H*-6-indazolylamino)-6-methyl-N-(3-pyridylmethyl)nicotin**

**amide**

The desired compound (yield 58%) was prepared at the same manner as example 11, except for using 3-(aminomethyl)pyridine instead of cyclopropyl amine. Then crude product was purified by recrystallization with chloroform : isopropyl ether=1:2 (v/v).

m.p. : 170~172 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49 (s, 3H), 4.52 (s, 2H), 6.78 (d, 1H), 6.94 (d, 1H), 7.37 (dd, 1H), 7.60 (d, 1H), 7.91 (s, 1H), 8.11 (d, 1H), 8.48 (d, 1H), 8.51 (s, 1H), 8.58 (s, 1H), 9.31 (br s, 1H), 11.24 (s, 1H), 12.81 (br s, 1H)

**<Example 20> Preparation of  
N-[3-(1H-1-imidazolyl)propyl]-2-(1H-6-indazolylamino)-6-methylnicotinamide**

The desired compound (yield 65%) was prepared at the same manner as example 14, except for using 1-(3-aminopropyl)imidazole instead of 4-(2-aminoethyl)morpholine. Then crude product was purified by recrystallization with ethanol : isopropyl ether=1:3 (v/v).

m.p. : 203~205 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 1.99 (m, 2H), 2.49 (s, 3H), 3.34 (m, 2H), 4.04 (m, 2H), 6.78 (d, 1H), 6.89 (s, 1H), 6.95 (d, 1H), 7.22 (s,

1H), 7.61(d, 1H), 7.67(s, 1H), 7.91(s, 1H), 8.05(d, 1H), 8.53(s, 1H), 8.73(br s, 1H), 11.24(s, 1H), 12.81(br s, 1H)

<Example 21> Preparation of  
2-(1*H*-6-indazolylamino)-6-methyl-N-(2-pyridyl)-3-pyridineca  
5 bohydrazide

To the solution of 2-(1*H*-6-indazolylamino)-6-methylnicotinic acid 1.0 g obtained by preparation example 2 in acetonitrile 30 ml was added thionyl chloride 0.83 ml slowly. After stirring at 70 °C for 1 hr, the 10 reaction mixture was cooled. Then 2-hydrazinopyridine 2.7 g was slowly added at 0~5 °C and the mixture was stirred for 30 min. The reaction mixture was diluted with methanol 10 ml and methylene chloride 10 ml, stirred for 10 min., and then filtered. The filterate was concentrated under reduced pressure and the residue 15 was dissolved in methanol 10 ml. To the solution were slowly added H<sub>2</sub>O 20 ml and 3N-NaOH aqueous solution a little to adjust to pH=8. The solution was stirred for 2 hr and filtered to obtain the solid. The filtered product was washed with H<sub>2</sub>O : methanol=4:1(v/v) and dried at 40~50 °C in vacuo to obtain the 20 desired compound (1.03 g, yield 77%).

m.p. : 143~145 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49(s, 4H), 6.67~6.72(m, 2H),

6.79(d, 1H), 6.93(d, 1H), 7.51~7.59(m, 2H), 7.89(s, 1H), 8.06(d, 1H), 8.16(m, 1H), 8.48(s, 1H), 8.55(br s, 1H), 10.54(br s, 1H), 10.87(s, 1H), 12.80(br s, 1H)

5      <Example                          22>                          Preparation                          of

2-(1*H*-6-indazolylamino)-6-methyl-N-(3-pyridylcarbonyl)-3-pyridinecarbohydrazide

The desired compound (yield 69%) was obtained by performing at the same manner as example 21, except for using nicotinic hydrazide instead of 2-hyrazinopyridine.

10     m.p. : 244~246 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49(s, 3H), 6.83(d, 1H), 6.98(d, 1H), 7.60(m, 2H), 7.91(s, 1H), 8.15(d, 1H), 8.28(d, 1H), 8.52(s, 1H), 8.79(d, 1H), 9.09(s, 1H), 10.79~10.84(m, 3H), 12.83(br s, 1H)

15     <Example                          23>                          Preparation                          of                          2-(1*H*-6-indazolylamino)-6-methyl-3-(4-morpholinylcarbonyl)pyridine

The desired compound (yield 64%) was prepared at the same manner as example 14, except for using morpholine instead of 20 4-(2-aminoethyl)morpholine. Then crude product was purified by recrystallization with methylene chloride : n-hexane=1:1(v/v).

m.p. : 103~104 °C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), ppm : δ 2.49(s, 3H), 3.33(m, 4H), 3.57(m, 4H), 6.76(d, 1H), 7.12(d, 1H), 7.53(d, 1H), 7.58(d, 1H), 7.89(s, 1H), 8.20(d, 1H), 8.63(br s, 1H), 12.76(br s, 1H)

**<Experiment 1> Inhibitory effect on the *in vitro* activities of HBV polymerase in reverse transcription**

The following *in vitro* experiment was performed to determine the effect of the compounds of formula 1 on the activity of HBV polymerase during reverse transcription.

The present inventors submitted application for a patent concerning HBV polymerase genetically expressed in and separated from *E. coli*, the process of its preparation, and the method to measure the enzyme activities (KR 94-3918, KR 96-33998). In the present experiments HBV polymerase was used which had been expressed in *E. coli* as stated above.

The method used in the present invention to measure *in vitro* reverse transcribing activities of HBV polymerase is as follows. Basic principles are the same as those for ELISA, nucleotides with biotin- or digoxigenin- group are included as substrates and anti-DIG antibodies attached to peroxidase enzyme recognize the polymerized substrates.

To the wells coated with streptavidin, 20 μl of HBV polymerase, 20 μl of reaction mixture (10 μM each of DIG-UTP and

Biotin-UTP, 46 mM Tris-HCl, 266 mM KCl, 27.5 mM MgCl<sub>2</sub>, 9.2 mM DTT substrate/primer hybrid), and 20  $\mu$ l of test compound (added to 1, 0.1, and 0.01  $\mu$ g/ml) were added and allowed to react at 22°C for 15 hrs. During this reaction, HBV polymerase catalyzes 5 DNA synthesis, and digoxigenin and biotin attached to nucleotides form bonds to streptavidin coated on the bottom of wells. When the reaction was done, each well was washed with 250  $\mu$ l of cleaning buffer (pH 7.0) for 30 seconds, which was repeated five times to remove remaining impurities. 200  $\mu$ l of anti-DIG-POD antibody 10 was added to each well and allowed to react for 1 hr at 37°C, and the wells were washed with cleaning buffer to remove impurities. 200  $\mu$ l each of ABTS™, a substrate of peroxidase, was then added and allowed to react at room temperature for 30 min. Absorbancy was measured at 405 nm using ELISA reader.

15 The inhibitory effects in HBV polymerase activities for reverse transcription were calculated using the group without test compound as a control and the results are shown in Table 1 as follows.

TABLE 1. Inhibitory effect on the HBV polymerase activities in reverse transcription

Compound	Inhibitory activity on HBV-RT (%)		
	1 $\mu\text{g}/\text{ml}$	0.1 $\mu\text{g}/\text{ml}$	0.01 $\mu\text{g}/\text{ml}$
Example 1	78	49	30
Example 2	88	57	42
Example 3	80	61	53
Example 4	92	64	50
Example 5	65	43	37
Example 6	84	55	40
Example 7	70	50	21
Example 8	78	54	23
Example 9	65	48	20
Example 10	89	62	48
Example 11	84	54	32
Example 12	86	60	49
Example 13	54	45	15
Example 14	91	68	52
Example 15	87	57	12
Example 16	78	51	35
Example 17	86	56	24
Example 18	69	40	18
Example 19	76	48	32
Example 20	88	59	47
Example 21	86	50	30
Example 22	85	54	26
Example 23	62	40	12

As shown in Table 1, the compounds of the present invention have excellent inhibitory effects on the HBV polymerase activities and the maximum result showed 92% inhibition at the concentration of 1  $\mu\text{g}/\text{ml}$ . Moreover, the compounds of the present invention are non-nucleoside compounds, so they are not expected to have problems such as toxicity and early appearance of

resistant viruses as observed in the use of nucleosides and may be applied together with nucleoside compounds due to different mechanisms of action.

In summary, the compounds of the present invention  
5 effectively reduce the activities of HBV polymerase that plays the important role in the replication of HBV, and as the result, they could inhibit replication and proliferation of HBV and may be useful as a therapeutic agent for prevention and treatment of hepatitis B.

10 **<Experiment 2> Inhibitory effect on the *in vitro* HCV activity in RNA-dependant RNA-polymerase.**

The following *in vitro* experiment was performed to determine inhibitory effects of compounds of formula 1 on the activity in RNA-dependant RNA-polymerase.

15 To test *in vitro* for HCV activity in RNA-dependant RNA-polymerase, the following experiment was carried out.

First, 10  $\mu$ l of HCV NS5B(RNA-polymerase) and 25  $\mu$ l of reaction buffer solution [Tris·Cl (pH 7.5) 0.1 M, NaCl 0.1 M, MgCl<sub>2</sub> 0.01 M, KCl 0.2 M, EDTA 0.002 M, DTT 0.05 M] were added  
20 to a well coated with streptavidin. 10  $\mu$ l of reaction mixture containing poly A/UTP, as a RNA template-primer, DIG-UTP, biotin-UTP and UTP were added and subsequently test compounds

prepared were also added at the final concentration of 10, 1 and 0.1 µg/ml. The mixture was allowed to react 22 °C for 1 hr. The inhibitory activity was measured in comparison with negative control without the test compounds. At this time, RNA was formed 5 from RNA by the action of HCV polymerase, forming bonds with streptavidin coated on the bottom of wells due to dioxigenin and biotin attached to nucleotides. When the reaction was completed, each well was washed with 200 µl of washing buffer (pH 7.0) for 30 sec. three times to remove remaining impurities. 10 200 µl of anti-DIG-POD antibody was added to each well and allowed to react for 1 hr at 37°C, and the wells were washed with cleaning buffer to remove impurities. 200 µl of ABTS™, a substrate for peroxidase(POD), was added to each well, allowed to react at room temperature for 30 min., and absorbance at 405 nm was measured 15 for each solution using ELISA reader.

The percentage of inhibition effect in the activity of HCV RNA polymerase, was calculated using the negative control without the test compounds and the results are represented in Table 2. as follows.

TABLE 2. Inhibitory effect on the HCV proliferation

Compound	Inhibition activity on HBV-RT (%)		
	1 $\mu\text{g}/\text{ml}$	0.1 $\mu\text{g}/\text{ml}$	0.01 $\mu\text{g}/\text{ml}$
Example 1	59	38	12
Example 2	83	54	40
Example 3	90	61	46
Example 4	63	41	24
Example 5	52	37	10
Example 6	81	55	37
Example 7	65	52	15
Example 8	60	47	27
Example 12	82	68	43
Example 14	74	53	35
Example 16	90	67	54
Example 17	65	42	31
Example 18	63	43	15
Example 19	65	47	32
Example 20	59	42	16
Example 21	85	58	20
Example 22	55	35	20

As shown above in Table 2, it is found that the compounds of the present invention have excellent inhibitory effect on 5 90% inhibition at the concentration of 10  $\mu\text{g}/\text{ml}$  and approximately 60% at 1  $\mu\text{g}/\text{ml}$ . Consequently, the compounds of the present invention effectively reduce the activities of HCV RNA-polymerase that plays the important role in the replication of HCV, and as the result, they could inhibit replication and 10 proliferation of HCV and may be useful as a therapeutic agent

for prevention and treatment of hepatitis C. Moreover, it is expected that the compounds of the present invention, being non-nucleotides, do not have problems such as toxicity and early appearance of resistant strains observed in the use of nucleoside substrates, furthermore may be used together with them since the mechanism differs from that of nucleotide compounds.

**<Experiment 3> Inhibitory effect on the *in vitro* HIV enzyme activities in reverse transcription**

The following *in vitro* experiments were done to determine 10 the effect of compounds of formula 1 on the inhibitory effect of HIV enzyme activities in reverse transcription.

Non-radioactive reverse transcriptase assay kit (Boehringer Mannheim) was used in the measurement of *in vitro* transcriptase activities. 20  $\mu\text{l}$  (40 ng) of HIV reverse transcriptase and 20  $\mu\text{l}$  of reaction mixture containing 15 matrix-primer hybrid poly(A) oligo(dT)<sub>15</sub>, DIG(digoxigenin)-dUTP, biotin-dUTP, dTTP were added to wells coated with streptavidin, and the test compounds prepared were also added at the final concentrations of 0.1 and 1  $\mu\text{g}/\text{ml}$  and allowed to react at 37°C 20 for 1 hr. At this time, DNA is formed from RNA by the action of HIV reverse transcriptase, forming bonds with streptavidin coated on the bottom of wells through digoxigenin and biotin

moieties attached to nucleotides.

When the reaction was completed, each well was washed with 250  $\mu$ l of washing buffer (pH 7.0) for 30 sec. five times to remove remaining impurities. 200  $\mu$ l of anti-DIG-POD antigen was added 5 to each well, then the mixture was allowed to react at 37 °C for 1 hr and washed as above to remove impurities. 200  $\mu$ l of ABTS<sup>TM</sup>, a substrate for peroxidase, was added to each well and the mixture was allowed to react at room temperature for 30 min. Absorbance at 405 nm was measured for each solution using ELISA 10 reader to determine the inhibitory effect on the HIV reverse transcriptase activities. The percentage of inhibition in the activity of HIV reverse transcriptase was calculated using the group without test compound as control and the results are represented in Table 3.

15

TABLE 3. Inhibitory effect on the activity of HIV reverse transcriptase

Compound	Inhibition activity on HIV-RT (%)	
	1 µg/ml	0.1 µg/ml
Example 1	75	42
Example 2	84	49
Example 3	80	51
Example 4	64	40
Example 5	69	38
Example 6	77	45
Example 8	65	28
Example 11	82	45
Example 14	70	41
Example 15	78	43
Example 17	84	50
Example 20	88	47
Example 21	75	49

As shown above in Table 3, it is found that the compounds  
 5 of the present invention have excellent inhibitory effect on  
 the activities of HIV reverse transcriptase, having more than  
 up to 80% inhibition at the concentration of 1 µg/ml, and  
 approximately 50% at 0.1 µg/ml. Consequently, the compounds of  
 the present invention effectively reduce the activities of HIV  
 10 reverse transcriptase that plays the important role in the  
 replication of HIV, and as the result, they could inhibit  
 replication and proliferation of HIV and may be useful as a  
 therapeutic agent for prevention and treatment of AIDS.

Moreover, it is expected that compounds of the present invention, being non-nucleosidic, do not have problems such as toxicity and early development of resistant virus strains observed in the use of nucleotide substances. Furthermore, The 5 compounds of the present invention may be used together with nucleoside compounds since the former act on allosteric binding pockets while the latter act in the domain of polymerase activities.

**<Experiment 4> Cytotoxicity test**

10 To determine if compounds of formula 1 exhibit cytotoxicity, *in vitro* tests were carried out using HepG2 cells with MTT analysis method as generally known.

15 As a result, all of the compounds used in the experiments have higher than 100  $\mu\text{g}/\text{ml}$  for CC<sub>50</sub> and are considered to have little cytotoxicity.

**<Experiment 5> Acute toxicity in rats tested via oral administration**

The following experiments were performed to see if compounds of formula 1 have acute toxicity in rats.

20 1) The compounds obtained from the example 1~6

6-week old SPF SD line rats were used in the tests for acute toxicity. The compounds in the examples of 1~6 were

suspended in 0.5% methylcellulose solution and orally administered once to 6 rats per group at the dosage of 2 g/kg/15ml. Death, clinical symptoms, and weight change in rats were observed. Hematological tests and biochemical tests of blood were performed  
5 and any abnormal signs in the gastrointestinal organs of chest and abdomen were checked with eyes during autopsy. The results showed that the test compounds did not cause any specific clinical symptoms or death in rats and no change was observed in hematological tests, weight change, blood tests, biochemical tests of blood, and autopsy. As a results, the compounds of the example 1~6 used in this experiment, are evaluated to be safe substances since they do not cause any toxic change in rats up to the level of 2 g/kg and the LD<sub>50</sub> values are much greater than 2 g/kg in rats.

15 2) The compounds obtained from the example 7~23

Acute toxicity was carried out through oral administration once to 6-week old SPF SD line rats per group at the dosage of 3 g/kg/15ml , as a result, the compounds of the example 7~23 were considered to be safe since they do not cause any toxic change  
20 in rats up to the level of 3 g/kg , the LD<sub>50</sub> values are much greater than 3 g/kg in rats.

INDUSTRIAL APPLICABILITY

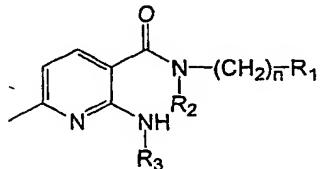
As described above, novel 6-methylnicotinamide derivatives represented by formula 1 of the present invention have the dramatic inhibitory effect on proliferation of HBV, 5 HCV and HIV with little side effect and may be useful as therapeutic agents for prevention and treatment of hepatitis B and C, and AIDS. Moreover, it is expected that compounds of the present invention, being non-nucleosidic, do not have problems such as toxicity and early development of resistant virus strains 10 observed by nucleoside substances. Furthermore, compounds of the present invention may be used together with nucleoside compounds since the former seem to act on allosteric binding pockets while the latter work in the domain of polymerase activities.

15

**WHAT IS CLAIMED IS;**

1. 6-methylmicotinamide derivatives of formula 1 or their pharmaceutically acceptable salts:

Formula 1



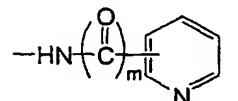
5

wherein,

R<sub>1</sub> is hydroxy; straight or branched C<sub>1</sub>~C<sub>5</sub> alkyl group;

C<sub>3</sub>~C<sub>6</sub> cycloalkyl group which is unsubstituted or substituted with hydroxy, C<sub>2</sub>~C<sub>6</sub> dialkylamino group;

10 saturated or unsaturated 5 or 6 membered heterocyclic compounds containing 1 to 2 heteroatoms selected from N, O and S which may be unsubstituted



or substituted C<sub>1</sub>~C<sub>3</sub> alkyl group; or

m is an integer of 0 or 1,

15 R<sub>2</sub> is H or C<sub>1</sub>~C<sub>4</sub> alkyl group;

or R<sub>1</sub> and R<sub>2</sub> are joined to form a 5- and 6-membered heterocyclic ring containing 1 to 2 hetero atoms selected from N, O and S,

n is an integer from 0 to 4,

20 R<sub>3</sub> is 5-indazole or 6-indazole.

2. The 6-methylmicotinamide derivatives or their pharmaceutically acceptable salts according to claim 1, wherein,

R<sub>1</sub> is hydroxy, methyl, isopropyl,  
5 t-butyl, cyclopropyl, 4-hydroxy-1-cyclohexyl,  
dimethylamino, 4-morpholinyl, 1-piperidinyl,  
4-methyl-1-piperazinyl, 2-pyridyl, 3-pyridyl,  
1-imidazolyl, 2-pyridylamino, or  
3-pyridylcarbonylamino;

10 R<sub>2</sub> is H;

n is an integer from 0 to 3.

3. The 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts according to  
15 claim 1, wherein the 6-methylnicotinamide derivatives represented by formula 1 are selected from the group consisting of:

- 1) 2-(1*H*-5-indazolylamino)-*N*-isopropyl-6-methylnicotinamide,
- 20 2-(1*H*-5-indazolylamino)-6-methyl-*N*-(4-morpholinyl)nicotinamide,
- 3) *N*-(*trans*-4-hydroxy-1-cyclohexyl)-2-(1*H*-5-indaz

- o<sub>2</sub>ylamino)-6-methylnicotinamide,
- 4) 2-(1H-5-indazolylamino)-6-methyl-N-(3-pyridyl)nicotinamide,
- 5) 2-(1H-5-indazolylamino)-6-methyl-N-(3-pyridylmethyl)nicotinamide,
- 6) 2-(1H-5-indazolylamino)-6-methyl-N-(2-pyridylethyl)nicotinamide,
- 7) 2-(1H-6-indazolylamino)-6-methyl-N-methylnicotinamide,
- 10 8) 2-(1H-6-indazolylamino)-N-isopropyl-6-methylnicotinamide,
- 9) N-(t-butyl)-2-(1H-6-indazolylamino)-6-methylnicotinamide,
- 15 10) N-(2-hydroxyethyl)-2-(1H-6-indazolylamino)-6-methylnicotinamide,
- 11) N-cyclopropyl-2-(1H-6-indazolylamino)-6-methylnicotinamide,
- 12) N-[2-(dimethylamino)ethyl]-2-(1H-6-indazolylamino)-6-methylnicotinamide,
- 20 13) N-[2-(diethylamino)ethyl]-2-(1H-6-indazolylamino)-6-methylnicotinamide,
- 14) 2-(1H-6-indazolylamino)-6-methyl-N-[2-(4-morp

holinyl)ethyl]nicotinamide,

15) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(2-(1-pipe  
ridinyl)ethyl]nicotinamide,

16) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(4-morphol  
5 inyl)nicotinamide,

17) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(4-methyl-  
1-piperazinyl)nicotinamide,

18) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(3-pyridyl  
10 )nicotinamide,

19) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(3-pyridyl  
methyl)nicotinamide,

20) *N*-[3-(1*H*-1-imidazolyl)propyl]-2-(1*H*-6-indazol  
ylamino)-6-methylnicotinamide,

21) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(2-pyridyl  
15 )-3-pyridinecarbohydrazide,

22) 2-(1*H*-6-indazolylamino)-6-methyl-*N*-(3-pyridyl  
carbonyl)-3-pyridinecarbohydrazide, and

23) 2-(1*H*-6-indazolylamino)-6-methyl-3-(4-morphol  
20 inylcarbonyl)pyridine.

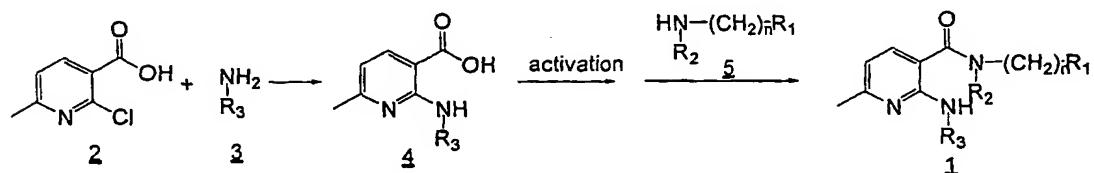
4. A process for preparing 6-methylnicotinamide derivatives according to claim 1 comprising the

following steps of:

1) preparing of 6-methylnicotinic acid derivatives (4) substituted with aminoindazole by reacting 2-chloro-6-methylnicotinic acid (2) with 5-aminoindazole or 6-aminoindazole (3) in the presence of a base; and,

2) preparing of 6-methylnicotinamide derivatives of formula 1 by activating the 6-methylnicotinic derivatives (4) prepared in step 1, and then reacting the compounds of formula 4 with amine compound (5);

Scheme 1



wherein, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and n are defined in formula 1.

5. The process according to claim 4, wherein the activation is performed by activating highly reactive acid chloride compound, adding a bit excess thionyl chloride to 6-methylnicotinic acid derivative(4), subsequently heating, or, by Vilsmeier reagent prepared for heating thionyl

chloride and N,N-dimethylformamide.

6. A therapeutic agent or a preventive agent for hepatitis B, comprising 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts of claim 1 as effective ingredients.
7. A therapeutic agent or a preventive agent for hepatitis C, comprising 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts of claim 1 as effective ingredients.
8. A therapeutic agent or a preventive agent for acquired immune deficiency syndrome (AIDS), comprising 6-methylnicotinamide derivatives or their pharmaceutically acceptable salts of claim 1 as effective ingredients.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 01/078648 A3

(54) Title: 6-METHYLNICOTINAMIDE DERIVATIVES AS ANTIVIRAL AGENTS

(57) Abstract: The present invention relates to novel 6-methylnicotinamide derivatives and their pharmaceutically acceptable salts, the process for preparing them, and the pharmaceutical compositions containing said compounds as active ingredients. The 6-methyl-nicotinamide derivatives of the present invention exhibit their inhibitory activity against the proliferation of human immunodeficiency virus (HTV) as well as hepatitis B virus (HBV) and Hepatitis C virus (HCV), such that they can be used for hepatitis B, hepatitis C and acquired immune deficiency syndrome (AIDS).

# INTERNATIONAL SEARCH REPORT

National application No.

PCT/KR01/00613

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC7 C07D 401/12**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
Korean Patent and applications for inventions since 1983

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CA PLUS(STN), REGISTRY(STN)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97-3071 A1(KNOLL AKTIENGESELLSCHAFT) 30 JANUARY 1997, SEE THE WHOLE DOCUMENT	1 - 3
A	US 5424432 A(MERCK AND Co., Inc.) 13 JUNE 1995, SEE THE WHOLE DOCUMENT	1
A	DEMINA, L. M.; DANILOVA, V. K 'Alkylamides of 2-chloro- and 2-arylamino-4,6-dimethylnicotinic acid: Synthesis and Anticonvulsant activity', Perm. Farm. Inst., Russia, Khim.-Farm. Zh. 1993, 27(7), 34 - 5	1 - 3
A	SLADOWSKA, H.; ZAWISZA, T. 'Synthesis and Biological Activity of Alkylamides of 2-arylamino-6-methylnicotinic acids' Farm. Inst., Perm, USSR, Khim.-Farm. Zh. 1981, 15(4), 35-8	1 - 3

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

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Form PCT/ISA/210 (patent family annex) (July 1998)

